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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,126	02/22/2002	Gerald W. DeVries	17413(AP)	8539

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/081,126	DEVRIES, GERALD W.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/18/07 has been entered.

2. Claims 41-57 are pending and are being acted upon in this Office Action.

3. New Ground of objection and rejections.

4. Claims 53-57 are objected to because said claims dependent from canceled claim 39.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 41-48, and 52-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yatoh et al (Transplantation 66(11): 1519-1524, 1998; PTO 892) in view of Mimura et al (Exp Eye Res 72: 71-78, 2001; PTO 1449) and Kirkin et al (Eur J Biochem 268: 5530-5540, 2001; PTO 1449).

Yatoh et al teach systemic injection and/or topical administration of immunosuppressive agent such as corticosteroids, cyclosporine, and FK-506 have been used postoperatively to prolong corneal graft (see page 1519, in particular). Yatoh et al further teach a method of extending corneal graft survival following corneal transplantation by topically administering to a patient such as a rat an effective amount of a pharmaceutical composition comprising an anti-angiogenic agent such as an anti-VEGF neutralizing antibody that inhibits VEGF from binding to its VEGF receptor (see entire document, Figure 2E and Table 2, in particular). Yatoh et al teach anti-VEGF antibody treated grafts survived significantly longer than saline or unrelated antibody treated grafts because VEGF mediates angiogenesis, vascular permeability immune-mediated

cells infiltration into the allograft and acute corneal inflammation are inhibited (see Discussion, in particular). Yatoh et al teach administering neutralizing VEGF antibody may be a new potential therapeutic strategy for treatment of corneal transplantation and the combined therapy with the topical immunosuppressive agents will increase the survival rate and suppress the angiogenesis in the corneal graft (see last paragraph in Discussion, in particular).

The invention in claim 41 differs from the teachings of the reference only in that the method of extending corneal graft by administering a compound selected from the group consisting of 3(2,4-dihydroxy-benzylidene)-1,3-dihydro-indol-2-one; 3-(3-fluoro-4-methoxy-benzylidene)-1,3-dihydro-indol-2-one; and 3-(4-dimethylamino-naphthalen-1-yl methylene)-1,3-dihyd ro-indol-2-one.

The invention in claim 42 differs from the teachings of the reference only in that the method of extending corneal graft by administering a compound 3(2,4-dihydroxy-benzylidene)-1,3-dihydro-indol-2-one.

The invention in claim 43 differs from the teachings of the reference only in that the method of extending corneal graft by administering a compound 3-(3-fluoro-4-methoxy-benzylidene)-1,3-dihydro-indol-2-one.

The invention in claim 44 differs from the teachings of the reference only in that the method of extending corneal graft by administering a compound 3-(4-dimethylamino-naphthalen-1-yl methylene)-1,3-dihyd ro-indol-2-one.

Mimura et al teach VEGF-C and VEGFR-3 are pathophysiologically relevant in the corneal lymphangiogenesis after injury (see page 77, col. 1, first paragraph, in particular). Mimura et al teach exogenous application of VEGF-C has been shown to induce growth of both blood vessels and lymphatic vessels in vivo and VEGFR-2 and VEGFR-3 and these responses are mediated by VEGFR-2 and VEGFR-3 expressed on vascular endothelial cells and lymphatic endothelial cells, respectively.

Kirkin et al teach a method of inhibiting lymphangiogenesis mediated by VEGF-C by blocking VEGFR-3 activation. The reference method comprises administering various tyrosine kinase inhibitors or indolinone compounds which mimics and competes with ATP binding in a number of receptor tyrosine kinase such as MAE87 which also known as 3(2,4-dihydroxy-benzylidene)-1,3-dihydro-indol-2-one, MAE106 also known as 3-(3-fluoro-4-methoxy-benzylidene)-1,3-dihydro-indol-2-one, and MAZ51 also known as 3-(4-dimethylamino-naphthalen-1-yl methylene)-1,3-dihyd ro-indol-2-one (see page 5537 and 5538, col. 2, in

particular). Kirkin et al teach MAE106 and MAZ51 specifically inhibit VEGF-C and VEGF-D induced activation of VEGFR-3 but not VEGFR-2 (see page 5538, col. 2, first paragraph, in particular). Kirkin et al teach these compounds may be useful for treat angiogenesis mediated diseases such as tumor metastasis and blocking VEGFR-3 dependent events (see page 5538, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute and/or combine the neutralizing anti-VEGF antibody that is useful for extending corneal graft rejection of Yatoh et al for/with the indolinone compounds such as MAE87 which also known as 3(2,4-dihydroxy-benzylidene)-1,3-dihydro-indol-2-one, MAE106 also known as 3-(3-fluoro-4-methoxy-benzylidene)-1,3-dihydro-indol-2-one, and MAZ51 also known as 3-(4-dimethylamino-naphthalen-1-yl methylene)-1,3-dihyd ro-indol-2-one that inhibit lymphangiogenesis mediated by VEGF-C by blocking VEGFR-3 activation as taught by Kirkin et al since Mimura et al teach VEGF-C and VEGFR-3 are pathophysiologically relevant in the corneal lymphangiogenesis. The term "comprising" is open-ended. It expands the composition in the claimed method to include additional therapeutic agents. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Kirkin et al teach these compounds MAE87 which also known as 3(2,4-dihydroxy-benzylidene)-1,3-dihydro-indol-2-one, MAE106 also known as 3-(3-fluoro-4-methoxy-benzylidene)-1,3-dihydro-indol-2-one, and MAZ51 also known as 3-(4-dimethylamino-naphthalen-1-yl methylene)-1,3-dihyd ro-indol-2-one are VEGFR-3 specific inhibitors and may be useful for treat angiogenesis mediated diseases by blocking VEGFR-3 dependent events (see page 5538, col. 2, in particular). Mimura et al teach VEGFR-3 is expressed on lymphatic endothelial cells and both VEGF-C and VEGFR-3 are pathophysiologically relevant in the corneal lymphangiogenesis (see page 77, col. 1, first paragraph, in particular). Claim 47 is included in this rejection because administering the pharmaceutical composition before instead of after corneal transplant is an obvious variation of the teachings of Yatoh et al.

7. Claims 49-51 and 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yatoh et al (Transplantation 66(11): 1519-1524, 1998; PTO 892) in view of Mimura et al (Exp Eye Res 72: 71-78, 2001; PTO 1449) and Kirkin et al (Eur J Biochem 268: 5530-5540, 2001; PTO 1449) as applied to claims 41-48, and 52-55 and further in view of US Pat 6,699,493 (filed November 28, 2001, PTO 892).

The combined teachings of Yatoh et al, Mimura et al and Kirkin et al have been discussed supra.

The invention in claim 49 differs from the teachings of the references only in that the method of extending corneal graft survival wherein the pharmaceutical composition is administered two or more times.

The invention in claim 50 differs from the teachings of the references only in that the method of extending corneal graft survival wherein the pharmaceutical composition is repeated administration over a period of at least one month.

The invention in claim 51 differs from the teachings of the references only in that the method of extending corneal graft survival wherein the pharmaceutical composition is repeated administration over a period of at least six months.

The invention in claim 56 differs from the teachings of the references only in that the method of extending corneal graft survival wherein the pharmaceutical composition is injected locally.

The invention in claim 57 differs from the teachings of the references only in that the method of extending corneal graft survival wherein the pharmaceutical composition released from an intraocular or periocular implant.

The '493 patent teaches a method of reducing transplantation rejection in the eye by intraocular implanting in the eye a pharmaceutical composition comprising immunosuppressive agent such as FK-506 in a bioerodable polymer (see entire document, col. 2, lines 1-67, claims of the '493 patent, in particular). The placement of the implant such as intraocular and periocular are within the purview of one ordinary skill in the art (see col. 3, lines 28-67, in particular). The '493 patent teaches the advantage of locally delivery in the eye will achieve adequate intraocular drug concentrations and minimize numerous negative side effects associated with systemic immunosuppression (see col. 1, lines 37-45, in particular). Claim 49 is included in this rejection because administering the pharmaceutical composition more than once to achieve and maintain particular drug concentration before and/or after corneal transplant is within the purview of one of

ordinary skill in the art as taught by the '493 patent (see col. 4, lines 15-17, in particular). Claims 50-51 are included in this rejection because it is within the purview of one ordinary skill in the pharmaceutical art to administer more than once as needed such as over a period of least four weeks, or six months or longer as taught by the '493 patent (see col. 4, lines 1-15, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject locally or implant the pharmaceutical composition of Yatoh et al, Mimura et al and Kirkin et al in the eye so that the pharmaceutical composition is released intraocular or periocularly as taught by the '493 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '493 patent teaches that the advantage of locally delivery in the eye will achieve adequate intraocular drug concentrations while minimize numerous negative side effects associated with systemic immunosuppression (see col. 1, lines 37-45, in particular).

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

10. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Patent Examiner
Technology Center 1600
August 3, 200